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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/125,005	07/30/1998	DANIEL CAPUT	IVD-913	7322

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EXAMINER
UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
1642	25

DATE MAILED: 06/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/125,005	Caput et al
Examiner	**Art Unit**
Ungar	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 30, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-32 and 35-38* is/are pending in the application.

4a) Of the above, claim(s) *6-32 and 35-38* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-5* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed February 19, 2002 (Paper No. 18) and on January 30, 2003 (Paper No. 23 have been entered. Previously pending claims 33-34 have been canceled, claims 1 and 3 have been amended. Claims 1-5 are currently being examined.

Claim Rejections - 35 USC § 101

2. Claims 1-5 remain rejected under 35 USC 101 for the reasons previously set forth in Paper No. 15, Section 6, pages 2-4 and previously and is newly rejected for the reasons set forth below.

Applicant argues that the p73 polypeptide of SEQ ID NO:1 disclosed in WO 99/66946 is identical, amino acid for amino acid to the SR-p70 polypeptide, SEQ ID NO:6 and that enclosed is an exhibit showing residue by residue comparison.

It is noted that although the exhibit disclosing the residue comparison of SEQ ID NO:6 and p73 was not found in the file, a review of the Examiner's sequence search done previously revealed that SEQ ID NO:6 is identical, residue by residue to the p73 amino acid of WO99/66946.

Applicant further argues that Tominaga et al (Br. J. Cancer:2001, 84(1)57-63), previously submitted, notes on page 57 in right column, that p73 accumulates in tumor cells. The argument has been considered but has not been found persuasive because a

review of Tominaga et al reveals that in January of 2001, four years after the priority date of the instant application, the reference teaches that "Although the eventual implication of p73 in human cancer is not fully elucidated, it is essential to evaluate the specificity for the p53 humoral response" toward the new p53 homologue, p73 (p. 61, paragraph bridging columns 1 and 2). Further the reference concludes on page 63 that "the status of p73 in human cancer deserves to be more carefully analyzed." It is clear that in 2001, the role of p73 in cancer had not yet been fully determined and further research was required. Further, the reference in Tominaga et al is drawn to a 1999 paper by Ikawa et al (Cell Death and Differentiation, 1999, 6:1154-1161) a paper published two years after the priority date of the instant application. Although Applicant did not submit the paper referred to, Examiner was able to get a copy of the paper. It is noted that Ikawa et al specifically teach that the role of p73 in carcinogenesis and/or cancer progression remains ambiguous at the present time (p. 1156, col 2). The reference goes on to detail the research drawn to p73 in the last 2 years (page 1156 col 2 to page 1159 col 1) and concludes with the statement that "The results suggest that p73 is not a tumor suppressor gene in a classic Knudson manner".

Further, a review of the previous sequence search revealed seven different isoforms for p73 (see Attached sequence listing us-09-125-005-6.rsp, pages 1 and 2) and the Ikawa et al paper reveals six different isoforms. Although p73 alpha is expressed both in normal and tumor tissue, relative expression levels of p73 has been shown to be elevated in some cancer types compared to normal control but not in others (see p. 1157 col 2 and Table 2, p. 1158). However, although p73 alpha is expressed in both normal and tumor tissue, there is no teaching as to which of the

isoforms is overexpressed in the cancer types recited. In order to determine whether SEQ ID NO:6 is differentially expressed in tumors as compared to normal tissues, additional experimentation is required since it has not been determined whether alteration in expression of the claimed isoform would be in any way involved in any tumor in view of the fact that the function of the claimed isoform has not been established and that function cannot be predicted since the claimed isoform is an splice variant. The unpredictability of splice variant function is well known in the art. For example, Hirashima (Int. Arch. Allergy Immunol., 2000, Suppl 1:6-9) discloses that there are multiple isoforms of ecalectin/galectin-9 (page 8, first column second paragraph, lines 10-16), and "it cannot be excluded that each isoform exhibits different biological activity" (page 8, second column, lines 6-7). Benedict et al (J. Exp. Medicine, 2001, 193(1)89-99) specifically teach that two splice isoforms of terminal deoxynucleotidy transferase (a long form and a short form) enter the nucleus but have different activity, the long form does not catalyze nontemplated nucleotide addition but rather modulates the activity of the short form (see abstract). Jiang et al (JBC, 2003, 278(7) 4763-4769 specifically teach that the type 3 Ca2+ release channel, RyR3 exhibits strikingly different pharmacologic and functional properties depending on the tissues in which it resides. Upon examination, seven tissue specific alternatively spliced variants of RyR3 were detected. One of the variants was unable to form a functional channel but was able to suppress the activity of a different release channel. The authors conclude that tissue-specific expression of RyR3 splice variants is likely to account for some of the pharmacologic and functional heterogeneities of RyR3 (see abstract). These references serve to demonstrate that one of skill in the art cannot

predict the biological activity of splice variants based on the biological activity of the wild-type protein or a single protein isoform.

Finally, the teachings of Ikawa et al, *Supra* are drawn to the assay of nucleic acids which is not commensurate in scope with the claimed invention. Although the specification exemplifies the assay of various cell lines, including 8 tumor cell lines, for SR-p70, the protein was visualized only in a human glioblastoma and in a human colon adenocarcinoma cell line (see Figure 10(b). It cannot be determined from the teaching in the specification whether SEQ ID NO:6 is actually expressed *in vivo* or whether it is differentially expressed in tumor as compared to normal cells. The artifactural nature of cell lines is well known in the art. For example, Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. This is exemplified by the teachings of Zellner et al (Clin. Can. Res., 1998, 4:1797-17802) who specifically teach that products are overexpressed in glioblastoma (GBM)-derived cell lines which are not overexpressed *in vivo*. Drexler et al further teach that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the bona fide cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be

antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures in vitro frequently change their chromosomal constitutions (see abstract). Thus, based on the cell culture data presented in the specification, in the absence of data provided from primary tumor cells and normal controls, no one of skill in the art would believe it more likely than not that the claimed invention would have utility in a nexus to cancer. Further, as drawn to the production of protein *in vivo*, it is well known in the art that the regulation of mRNA translation is one of the major regulatory steps in the control of gene expression (Jansen et al, Pediatric Res., 1995, 37(6):681-686). Further, those of skill in the art, recognize that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into a polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation.

McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Thus, predictability of protein translation is not necessarily contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Thus, additional experiments must be done to determine if the claimed invention is even expressed *in vivo*. In view of the above, the claimed invention does not have substantial utility. Applicant's arguments have not been found persuasive and the rejection is maintained for the reasons of record and newly rejected for the reasons set forth above.

Claim Rejections - 35 USC § 112

3. Claims 1-5 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 15, Sections 7 and 8, pages 4-5 and previously.

Applicant argues that since the invention has utility for the reasons set forth above, the rejection should be withdrawn. The argument has been considered but has not been found persuasive for the reasons set forth above.

New Grounds of Objection

4. Claims 1-5 are objected to because claims 1-3 recite limitations drawn to non-elected inventions that have been withdrawn from consideration. Applicant is required

to amend the claims to delete all reference to non-elected inventions. Appropriate correction is required.

New Grounds of Rejection

Claim Rejections - 35 USC § 112.

5. Claims 1-5 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to SEQ ID NO:6. The specification teaches that SEQ ID NO:6 is expressed in three cell lines, two that are cancer cell lines and one that is a normal tissue cell line (see Figure 10(b). The specification further teaches that the protein is useful for prophylactic, therapeutic and diagnostic applications in the field of pathologies linked to the phenomena of apoptosis or of cell transformation (p. 1, lines 5-10). Further, because of the relationship to p53, the compositions of the invention afford a novel approach to treating the phenomena of carcinogenesis (p. 16, lines 12-14). One cannot extrapolate the teaching of the specification to the enablement of the claims because a review of the specification and the instant prosecution reveal that the identity between human p53 and SEQ ID NO:6 is 27% overall (see attached sequence comparison of human p53 and SEQ ID NO:6, u123006_6xp04637.res). Although the specification teaches that the greatest area of homology is found between amino acids 110 and 310, the DNA binding domain, a comparison of the two domains shows that this homology is 59%. It is clear that although there is an overall identity of 27%, there is also an overall dissimilarity of 73%. Even in the putative DNA binding

domain there is a 41% dissimilarity in amino acid constitution. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a

protein. Clearly, with 73% dissimilarity, to p53 overall and a 41% dissimilarity to p53 in the putative DNA binding region, the function of the SEQ ID NO:6 polypeptide could not be predicted, based on sequence similarity with p53, nor would it be expected to be the same as that of p53. It is very clear, given the teaching of the specification that the DNA binding domain of p53 permits binding to the specific DNA sequences located in the promoter regions of certain genes and that the N terminal domain is involved in the activation of transcription and contains sites for interaction with different cellular and viral proteins and that the C terminal domain is involved with oligomerization and regulation of oligomerization. It cannot be predicted, based upon the information known in the art, what effect changes in 41% of the DNA binding domain proteins will have upon DNA binding sites for specificity of binding or for target site elected and what effect changes of 71% overall will have on the function and activity of the protein . In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30%

of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399 para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Clearly, given not only the teachings of Bowie et al, Lazar et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, with a 73 % overall dissimilarity to p53 and with 41% dissimilarity in the putative DNA binding region, the function of the SEQ ID NO:6 polypeptide could not be predicted, based on sequence similarity with p53, nor would it be expected to be the same as that of p53. That is, even if the putative DNA binding domain binds to DNA, the sites of binding cannot be determined and would not be expected to mimic those of p53. Finally, Ikawa et al, *Supra*, specifically teach that the role of p73 in carcinogenesis and/or cancer progression remains ambiguous at

the present time (p. 1156, col 2). The reference goes on to detail the research drawn to p73 in the last 2 years (page 1156 col 2 to page 1159 col 1) and concludes with the statement that "The results suggest that p73 is not a tumor suppressor gene". Given the unknown function of the protein at the time the invention was made, it is clear that one would not know how to use the claimed invention.

In addition, although the specification clearly teaches that SEQ ID NO:6 can be used in a novel approach to treating the phenomena of carcinogenesis, it appears from the specification that SEQ ID NO:6 is the alpha splice variant of SR-p70 as the specification refers to SEQ ID NO:6 as SR-p70a (see Brief Description of Figure 6). Ikawa et al, *Supra*, specifically teach that there are six p73 isoforms generated by alternative splicing and that p73 alpha is ubiquitously expressed in brain, kidney, placenta, colon, heart, liver, spleen and skeletal muscle at low levels. The reference further teaches that p73 alpha transcripts are expressed both in most normal cell lines and in primary cancers and that in cancers the levels of p73 alpha expression are variable and generally low (p. 1157, col 2). Given the ubiquitous expression of p73 alpha, the generally low expression of p73 alpha in both normal and tumor tissues, it is unclear how one would use SEQ ID NO:6 in treating the phenomena of carcinogenesis or in the prophylactic, diagnostic or therapeutic methods suggested, especially when it is unknown whether p73 alpha protein is actually expressed *in vivo*. .

Further, although Tominaga et al, *Supra* teach the detection of autoantibodies to p73 in patients with various types of cancer, they do not teach which splice variant of SR-p70 the autoantibodies are specific for. Given the unpredictability of function for splice variants as taught by, Hirashima, Benedict et al and Jiang et al, it could not be

predicted, nor would it be expected that all splice variants would have either properties or function in common. The specification clearly teaches the western blotting for SR-p70 in cell lines with an anti-monkey SR-p70 antibody. The protein was visualized only in a human glioblastoma and in a human colon adenocarcinoma cell line (see Figure 10(b). It is noted that the antibody did not detect SR-p70a in the cell line from which SR-p70a had been isolated. Given the teaching in the specification, it cannot be determined whether SEQ ID NO:6 is actually expressed *in vivo*. Although the artifactural nature of cell lines is well known, as evidenced by, Drexler et al, Zellner et al, Embleton et al, Hsu above, it cannot be determined whether the lack of protein expression in HT-29 cells is an artifact of the cell line or whether the protein expression shown in the SW480 human colon adenocarcinoma cell line is an artifact. Given the teachings of Jansen, et al, Alberts et al, Shantz and Pegg, McClean and Hill , above, it clearly can't be predicted whether this splice variant is expressed *in vivo*, whether this splice variant is differentially expressed, whether this splice variant is involved with carcinogenesis or whether it can be used in methods drawn to the prophylactic, diagnostic or therapeutic methods suggested. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated, and if not, how to use the claimed invention with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

6. All other objections and rejections recited in Paper No. 15 are withdrawn.

7. No claims allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
June 3, 2003